REMARKS

Amendments to the Specification

The Office advised that the specification as electronically filed contains two identical page 19s. Applicants respectfully request that the Examiner delete one of the duplicate page 19s.

The specification at page 19 has been amended to correct grammatical errors and to correct the name of the PMO compound. Specifically, the word "phosphothioate" has been replaced with the word "phosphorodiamidate". The correct name associated with the term "PMO" was well known in the art at the time of filing. Accordingly, no new matter has been added by way of these amendments.

Amendments to the Claims

Claims 1-3, 6, 8-12, and 16 are currently pending. Claims 1, 2, 6, 8, and 10 have been amended. Claims 11, 12, and 16 have been canceled without prejudice or disclaimer. Claims 4-5, 7, 13-15, and 18-25 were previously withdrawn as drawn to a non-elected invention. Claim 17 was previously canceled without prejudice or disclaimer.

Claim 1 has been amended to recite that the first assay system comprises any of SEQ ID NOs: 1-6 and also to recite that the method comprises a second assay system capable of detecting a change in the PTEN/IGF pathway comprising cultured cells expressing RANBP2, contacting the second assay system with the test agent, and determining a change in the PTEN/IGF pathway in the second assay system. Support for the amendments can be found throughout the specification and in original claim 16.

Claim 2 has been amended to clarify that the assay system is the first assay system. Claim 6 has been amended to clarify that the assay system is the second assay system. Support for the amendments can be found throughout the specification.

Claim 8 has been amended to recite that the candidate test agent is a nucleic acid modulator. The scope of the claim was not changed by this amendment.

Claim 10 has been amended to recite that the nucleic acid modulator is a phosphorodiamidate morpholino oligomer (PMO). The correct name for PMO was known in the art at the time of filing.

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice, without intent to acquiesce in any rejection of record, and without intent to abandon any previously claimed subject matter. No new matter has been added by way of these amendments.

Oath/Declaration

Applicants note that the Office has objected to the Oath/Declaration on file. Applicants will submit a new Oath/Declaration in due course.

Claim Interpretation

Applicants note the comments made by the Office with respect to the word "purified" in claim 1. Applicants have amended claim 1 to recite an assay system comprising any of SEQ ID NOs: 1-6. Applicants believe that this amendment clarifies claim 1.

Rejection of Claims Under 35 U.S.C. § 112, second paragraph

Claims 1-3, 6, 8-12 and 16 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse the rejections.

The Office alleged that claims 1-3, 6, 8-12, and 16 were indefinite because it is unclear as to the metes and bounds of the term "RANBP2". Without acceding to the merits of the rejection, claim 1 has been amended to recite that the assay system comprises "any of SEQ ID NOs: 1-6", thereby obviating the rejection. Applicants respectfully request withdrawal of the rejection.

The Office also alleged that claim 10 is indefinite because it is unclear as to whether the Applicants meant to recite "phosphothioate" or "phosphorodiamidate" in referring to a "PMO". Applicants have amended claim 10 to recite "phosphorodiamidate", thereby obviating the rejection. Applicants respectfully request withdrawal of the rejection. Applicants note that the specification has been amended to make the same change. Applicant submit that the amendment has been made to describe

the term "PMO" in accordance with its customary usage by those of ordinary skill in the art. The name of the compound associated with the term "PMO" was known in the art at the time of filing. Accordingly, no new matter has been added by way of the amendment.

Rejections Under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1-3, 6, 8-12 and 16 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement, because the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Applicants respectfully traverse the rejections.

The Office asserted that the claims do not satisfy the written description requirement because the instant specification allegedly does not disclose a representative number of species of the genus RANBP2 nucleic acids that encode RANBP2 polypeptides with RANBP2 activity because it fails to teach what portions of RANBP2 are required for which activities, and which nucleic acid sequences that vary from SEQ ID NO: 1 will encode a functional RANBP2.

Applicants submit that the claims have been amended to recite a method of identifying a candidate PTEN/IGF pathway using an assay system capable of detecting RAN Binding Protein 2 (RANBP2) expression comprising any of SEQ ID NOs: 1-6. As amended, the claims require an assay system that detects the expression of a specified RANBP2 nucleic acid, irrespective of RANBP2 activity. In other words, the assay system is not measuring RANBP2 polypeptide activity, it is measuring the level of expression of a RANBP2 nucleic acid comprising any of SEQ ID NOs: 1-6. Given that the genus is limited to RANBP2 nucleic acids comprising any of SEQ ID NOs: 1-6 and the nucleotide sequences of those nucleic acids are provided, Applicants submit that the written description requirement is satisfied. Applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph, rejections based on a lack of written description.

Enablement

Claims 1-3, 6, 8-12, and 16 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement because the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Applicants respectfully traverse the rejections.

The Office argued that the present invention is not enabled because RANBP2 and nup358 share only 27% amino acid identity and one skilled in the art would appreciate that proteins with only 27% identity are likely to have functional differences. Thus, one skilled in the art would not necessarily assume that just because one of the proteins had a relationship with a given pathway, such as the PTEN/IGF pathway, the other protein did as well. Further, the Office argued that the claims read on a vast genus of variants, homologs, and orthologs, and the specification as filed fails to provide adequate description or guidance as to which variants, homologs, and orthologs would retain the required activity. Thus, the Office concluded that in view of the unpredictable nature of protein structure/function relationships, the lack of evidence linking RANBP2 to the PTEN/IGF pathway, the breadth of RANBP2 proteins encompassed by the claims, the lack of guidance regarding which structural features of RANPB2 would be necessary and sufficient to affect the PTEN/IGF pathway, and the lack of guidance as to how those structural features could be modified while retaining the requisite activity, one of skill in the art would have to perform undue experimentation in order to practice the invention.

Under 35 U.S.C. §112, all that is required for satisfaction of the enablement requirement is that the specification describe the invention in such terms as to enable one skilled in the art to make and use the invention. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *US v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); M.P.E.P. §2164.01. The contours of the "undue experimentation" standard have been outlined in several cases. The Federal Circuit has explained that "[t]he key word is 'undue' and not 'experimentation'. . . . The test is not merely quantitative, since a considerable amount of experimentation is

permissible, if it is merely routine." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); see also *Massachusetts Institute of Technology vs. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985) and *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

The claims as amended are drawn to a method of identifying a candidate PTEN/IGF pathway modulating agent comprising providing an assay system capable of detecting RANBP2 expression comprising any of SEQ ID NOs: 1-6, contacting the assay system with a test agent, determining a change in RANBP2 expression between the presence or absence of the agent to identify the agent as a candidate PTEN/IGF pathway modulating agent, providing a second assay system capable of detecting a change in the PTEN/IGF pathway, contacting the second assay system with the test agent, and determining a change in the PTEN/IGF pathway in the second assay system between the presence or absence of the test agent to confirm the test agent as a candidate PTEN/IGF pathway modulating agent.

Under 35 U. S. C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Contrary to the Office's allegation, the specification clearly teaches one skilled in the art how to make and use the claimed assay for identifying a candidate PTEN/IGF pathway modulating agent. First, the specification provides the sequences of various RANBP2 nucleic acids that can be used in the claimed assays. (Specification at, for example, pages 5-6). The specification also provides numerous examples of modulating agents that can be tested at, for example, pages 13-20. In addition, the specification clearly provides numerous examples of assays using RANBP2 nucleic acids that can be used to identify a candidate PTEN/IGF pathway modulating agent, including an agent that modulates RANBP2 expression. (Specification at, for example, pages 3-4, 20-28, 29-30, and 37-38). Further, the specification provides numerous examples of assays that can be used to confirm that the identified agent is a PTEN/IGF pathway

modulating agent. (Specification at pages 4, 20-30, and 38-39). Applicants submit that performing the assays described in the specification is within the skill of the ordinary artisan and would not be a matter of undue experimentation. Finally, the specification teaches various uses of the claimed methods at, for example, pages 33-34.

The Office alleges that the claimed assays are not enabled because there is insufficient evidence linking RANBP2 to the PTEN/IGF pathway. However, as discussed in the specification, the drosophila system is a well-accepted system for determining the function of mammalian genes. Due to a high level of gene and pathway conservation, the strong similarity of cellular processes and the functional conservation of genes between drosophila and mammals, identification of the involvement of genes in particular pathways and their functions in drosophila can be used effectively to determine correlative pathways and methods of modulating them in mammals. Specification at pages 2-3. In the present case, Applicants identified a gene that modifies the PTEN/IGF pathway in drosophila (CG11856) and identified its human homolog (RANBP2). One skilled in the art would reasonably accept Applicants' well-established methods and data concerning the link between RANBP2 and the PTEN/IGF pathway.

Furthermore, Applicants tested an RANBP2 nucleic acid modulator (RANBP2 siRNA) using various assay systems and demonstrated a link between RANBP2 and the PTEN/IGF pathway. The specification provides the results of siRNAs directed against RANBP2 RNA in various tumor cell lines (pages 37-39). These results show that the anti-RANBP2 siRNAs have an effect on: (1) cancer cell growth and survival; (2) induction of apoptosis; and (3) nuclear retention of FOXO. The data presented in the examples on pages 37-39 confirm the results observed in the original screen that identified RANBP2 and provides the nexus between the association of RANBP2 function to the PTEN/IGF pathway in humans that the Patent Office alleged is lacking. Specifically, Applicants demonstrated that RANBP2 is overexpressed in 50% of pancreatic cancer samples compared to tissue-matched control samples. Specification at pages 37-38. In addition, Applicants demonstrated that RANBP2 is involved in the proliferation of cancer cells, including 231T breast cancer cells, HCT116 colon cancer cells, and PC3 prostate cancer cells by showing that the inhibition of RANBP2 expression via siRNA causes a decrease in cancer cell proliferation. Specification at page 38. Further, using an MTS cell proliferation assay, Applicants demonstrated that

decreased RANBP2 expression (via RANBP2 siRNA) results in decreased proliferation in PC3 prostate cancer cells and A549 lung cancer cells. Specification at page 38. Also, standard colony growth assays revealed that decreased RANBP2 expression (via RANBP2 siRNA) results in a decrease in cell growth in HCT116 colon cancer cells, PC3 prostate cancer cells, A549 lung cancer cells, SW480 colon cancer cells, and RD1 Rhabdomyosarcoma cells. Specification at page 39. Additionally, decreased RANBP2 expression (via RANBP2 siRNA) results in apoptosis in A549 lung cancer cells. Specification at page 39. Finally, Applicants also showed that reduced expression of RANBP2 causes nuclear retention of FOXO, which suggests involvement of RANBP2 in the PTEN/IGF pathway. Specification at page 39. All of this additional data supports the initial finding of a link between RANBP2 and the PTEN/IGF pathway. Thus, one skilled in the art would readily believe that RANBP2 is associated with the PTEN/IGF pathway.

In view of the foregoing, as well as the amendments herein, the applicants request reconsideration and withdrawal of the rejection of claims 1-3, 6, 8-12, and 16 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Rejection of Claims Under 35 U.S.C. § 103

Claims 1, 2 and 8-10 were rejected under 35 U.S.C. 103(a) as obvious over Yokoyama et al (Nature, 376:184-188 (1995)), Bennett et al. (Curr. Opin. Mol. Ther. 1(3): 359-371, and Gerwitz (US 5,612, 212). Applicants respectfully traverse the rejections.

The Office stated that Yokoyama teaches a cDNA encoding RANBP2 and partially characterizes the function of the protein by inhibiting its activity in cultured cells through the use of RANBP2 antibodies. Citing Bennett et al., the Office stated that it was routine in the art at the time of the invention to investigate protein function by inhibiting expression of the protein through the use of antisense oligonucleotides. The Office further stated that Gewirtz teaches that the stability of antisense oligonucleotides can be improved by incorporating modifications such as phosphorothioate and morpholino linkages. The Office argued that it would have been obvious to one of ordinary skill in the art at the time of the invention to inhibit the expression of RANBP2 by administration of antisense oligonucleotides, including stabilized oligonucleotides,

because there was a desire to understand the function of RANBP2. The Office concluded that the present invention was obvious because all of the recited materials and method steps were known in the prior art, and there were sound scientific reasons for combining them in the way required by the instant claims.

However, to meet the requirements for a *prima facie* case of obviousness, the Office must demonstrate that the references teach or suggest all the limitations of the claims. Post-KSR, the Board of Patent Appeals and Interferences (BPAI) has continued to maintain that

> [A]n examiner must make "a searching comparison of the claimed invention — *including all its limitations* - with the teaching of the prior art." *In re Ochiai,* 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.,* 349 F.3d, 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka,* 490 F.2d 981, 985 (CCPA 1974)). *Ex Parte* Wada, BPAI, Appeal 2007-377, page 7 (Jan. 15, 2008) (unpublished).

See also, Ex parte Shepard, BPAI, Appeal 2008-0401, page 7 (Jan. 3, 2008)(unpublished).

Applicants submit that Yokoyama et al., Bennett et al., and Gewirtz et al., alone or in combination, fail to render the presently claimed methods obvious. None of the references teach or suggest a method of identifying a candidate PTEN/IGF pathway modulating agent using a first assay system comprising an RANBP2 nucleic acid and a second assay system capable of detecting a change in the PTEN/IGF pathway.

Although Yokoyama et al. describes RANBP2, it fails to recognize the connection between RANBP2 and the PTEN/IGF pathway. In fact, Yokoyama et al. makes no mention whatsoever of PTEN/IGF and therefore fails to even contemplate a method of identifying a candidate PTEN/IGF pathway modulating agent using an assay system that detects RANBP2 expression, much less teach or suggest the claimed methods. Neither Burnnett et al nor Gewirtz et al. cure the deficiencies of Yokoyama et al. Neither reference mentions RANBP2 or the PTEN/IGF pathway and thus they fail to teach or suggest the claimed methods.

In view of the fact that none of the cited references teach or suggest the claimed methods, they fail to render obvious the present invention. Accordingly, Applicants respectfully request withdrawal of the 35 USC 103 rejections based on Yokoyama et al., Bennett et al., and Gewirtz et al.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

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